First enantioselective total synthesis of (natural) (+)-11,12-epoxy-11,12-dihydrocembrene-C and (−)-7,8-epoxy-7,8-dihydrocembrene-C

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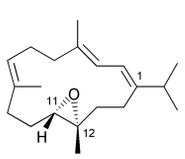
Received (in Cambridge, UK) 7th September 2000, Accepted 19th October 2000
First published as an Advance Article on the web 29th November 2000

The first enantioselective total syntheses of (+)-11,12-epoxy-11,12-dihydrocembrene-C **1** and (−)-7,8-epoxy-7,8-dihydrocembrene-C **2**, two naturally occurring cembranoxides isolated from tropical marine soft corals, are achieved *via* a general approach by employing an intramolecular McMurry coupling and Sharpless asymmetric epoxidation as key steps from readily available starting materials. The syntheses presented here verify the absolute stereochemistry assignment of **1** as (11*S*,12*S*) by Bowden *et al*. two decades ago, and the epoxy configuration of **2** was assumed as (7*R*,8*R*) accordingly.

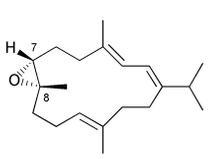
Introduction

Cembranoids belong to a structurally unique family of diterpene natural products characterized by the presence of a 14-membered ring, and have been isolated from various marine sources as well as some terrestrial organisms since the 1960s.[1] These diterpenoids have become of great interest to synthetic chemists and biologists because of their unusual structural features and remarkably wide range of biological activities.[2]

Naturally occurring cembranoid epoxides (cembranoxides) have been found as chemical components of various tropical marine soft corals and represent a class of oxidative metabolites of cembrane diterpenes. (+)-11,12-Epoxy-11,12-dihydrocembrene-C **1**, a novel cembrane epoxide, was first isolated in 1978 by Bowden *et al*.[3] from the Australian soft coral *Sinularia grayi*, and was subsequently found in various marine soft corals, *i.e*. *Nephthea* spp.,[4] *Lobophytum* spp.,[5,6] *Eunicea* spp.,[7a] and *Sinularia* spp.[7b] Its chemical structure was determined by means of extensive spectroscopic techniques and chemical degradation.[3] The absolute stereochemistry of the epoxide function of **1** was deduced[5] as (11*S*,12*S*) indirectly by Horeau's method.[8] (−)-7,8-Epoxy-7,8-dihydrocembrene-C **2** was first isolated in 1980 by Bowden *et al.* from the soft coral *Sarcophyton crassocaule*[9] and from the soft coral *Eunicea* spp.[7a] in 1993 by Shin and Fenical. Although its chemical structure was characterized spectroscopically, the absolute configuration of the epoxide moiety remains undetermined so far.



(+)-11,12-Epoxy-11,12-dihydrocembrene-C (**1**)



(–)-7,8-Epoxy-7,8-dihydrocembrene-C (**2**)

Stereoselective construction of the epoxide functionality in the macrocyclic cembrane skeleton comprises a challenging task for total synthesis. A general, simple and highly stereoselective synthetic method for the synthesis of cembranoxides such as **1** and **2** is highly desirable, as is the assignment of the absolute stereochemistry of the epoxide functions. In continuation of our ongoing programme on the asymmetric synthetic studies of cembranoids, we report details of the first total synthesis of **1** and **2** in this paper.[10]

General synthetic plan

The low-valent-titanium-induced intramolecular dicarbonyl olefination coupling (McMurry reaction)[11] is proven to be a valuable and versatile protocol for the construction of carbocyclic skeleta and has been illustrated in a great number of natural product syntheses as well as those of highly strained unnatural compounds.[11] The strong reducing conditions and extended reaction times normally used make the process incompatible with the easily reducible functional groups elsewhere in the substrate. A less reactive ester or lactone carbonyl in the substrate might survive under the usual conditions for the reductive olefination of the keto aldehyde precursors mediated by low-valent titanium and be left intact, although very few examples of this have been reported in the literature.[12,13]

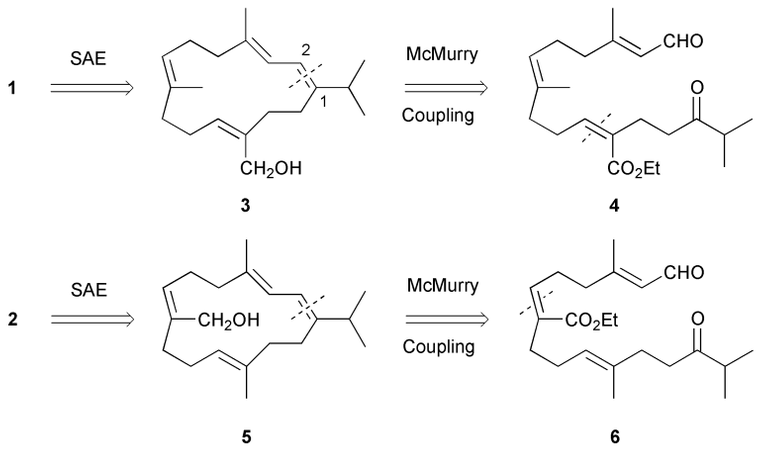
The general strategic plan was as depicted in Scheme 1. The epoxide functions of **1** and **2** would be assembled enantioselectively by Sharpless asymmetric epoxidation (SAE)[14] of the corresponding trisubstituted carbocyclic allylic alcohols **3** and **5**, respectively. Accordingly, the cembrane ring would be closed by means of the well developed intramolecular McMurry coupling of the keto aldehyde precursors **4** and **6**, respectively, which bear an α,β-unsaturated ester carbonyl assumed to be inert under the reaction condition. The precursors **4** and **6** could be fragmented into two pieces as shown and joined *via* Wadsworth–Horner–Emmons olefination leading to the α,β-unsaturated ester functionalities.

Results and discussion

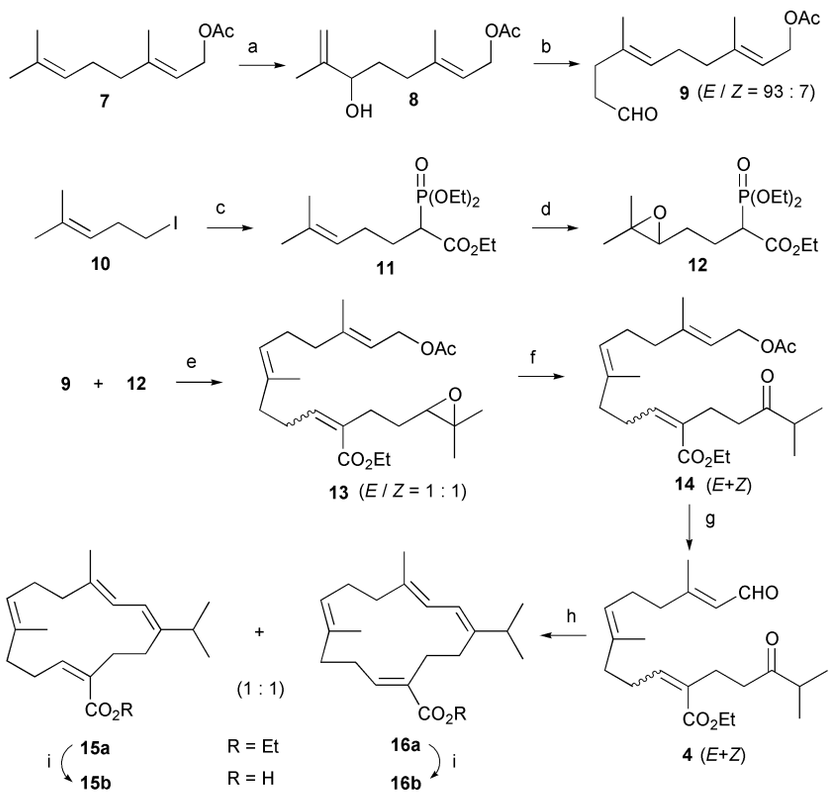
Enatioselective synthesis of (natural) (+)-11,12-epoxy-11,12-dihydrocembrene-C

The total synthesis of natural 11,12-epoxy-11,12-dihydrocembrene-C **1** is detailed in Scheme 2. Allylic alcohol **8**, readily available[15] from geranyl acetate **7** in four steps, was converted into the corresponding vinyl ether by a known procedure[16] catalyzed by $Hg(OAc)_2$, which was then subjected to thermal Claisen rearrangement[17] in a sealed tube at 110 °C to produce predominently the desired *E* aldehyde **9**[18] in the ratio 93:7 as determined by GLC. Homoprenyl iodide **10**[19] was transformed

 DOI: 10.1039/b007239g



Scheme 1



Scheme 2 *Reagents*, *conditions* (*and yields*): a) ref. 15; b) (1) $Hg(OAc)_2$, ethyl vinyl ether, reflux (83%); (2) sealed tube, 110 °C (90%); c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMF, 60 °C (88%); d) MCPBA, CH_2Cl_2, 0 °C (93%); e) LDA, −78 °C, 30 min; then aldehyde **9**, −78 °C to rt, 72%; f) $LiClO_4$, C_6H_6, reflux (81%); g) (1) K_2CO_3, MeOH, rt; (2) MnO_2, *n*-hexane, rt (72%); h) $TiCl_4$, Zn, THF, reflux (48%); i) KOH, EtOH–water, reflux (88–90%).

into phosphono ester **11** in 88% yield by a standard method,[20] and the product was then exposed to MCPBA in CH_2Cl_2 to give the epoxide **12** in 93% yield. The Wadsworth–Horner–Emmons coupling[20] of phosphono ester **12** with aldehyde **9** mediated by lithium diisopropylamide (LDA) led to ester **13** in 72% yield as a mixture of an equal amount of geometric isomers as determined by ^{1}H NMR analysis. Ketone **14** was obtained by the rearrangement[21] of the epoxide **13** (*E* + *Z*) catalyzed by $LiClO_4$. Saponification of **14** and subsequential MnO_2 oxidation (72%, two steps) gave the keto aldehyde **4**, which was added slowly *via* a syringe pump to a slurry of low-valent-titanium reagent (prepared *in situ* by the reduction of $TiCl_4$ with zinc powder) in THF under reflux over a period of 6 h to afford the desired carbocyclic ester **15a** and **16a** in the ratio 1 : 1 after silica gel column chromatography in a combined yield of 48%. Basic hydrolysis of the esters **15a** and **16a** gave acids **15b** and **16b** respectively, corresponding to crotocembraneic acid and neocrotocembraneic acid respectively,[22] two novel cembranoids isolated from the stem bark of the Thai traditional medicinal plant *Croton oblongifolius*, on the basis of spectroscopic comparison with the natural products.

Reduction of ester **15a** with $LiAlH_4$ in diethyl ether gave allylic alcohol **3** in 92% yield, which was epoxidized under Sharpless asymmetric epoxidation[14] conditions with diethyl D-tartrate (DET) to afford the epoxy alcohol **17** in 85% yield and 95% ee as determined by high-field ^{1}H NMR (400 MHz) analysis of the corresponding Mosher's ester[23] (Scheme 3). Standard iodination[24] of **17** (Ph_3P, imidazole, Py, I_2) and subsequent reductive dehalogenation[25] of the corresponding iodide intermediate with $NaBH_3CN$ in hexamethylphosphoric triamide (HMPA) produced the title compound **1**. The synthetic **1** showed identical spectroscopic properties (^{1}H, ^{13}C NMR) with those of the natural product, as well as a specific rotation {$[a]_D^{18}$ +109.1† (*c* 0.75 in $CHCl_3$)} similar to that reported for the natural product {$[a]_D$ +117 (*c* 0.09 in $CHCl_3$)}.[3]

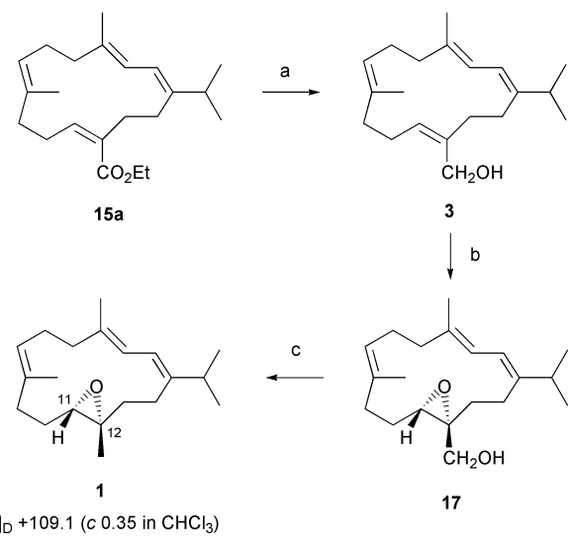
† Throughout this paper, specific optical rotations $[a]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.

Furthermore, the C-11 epimeric epoxide **1a** was synthesized in an analogous way from isomeric ester **16a** in an overall yield of 66% as shown in Scheme 4, and is distinguishable both spectroscopically as well as optically from synthetic **1**. The epoxy alcohol **19** was converted into **20**, *via* an iodization–rearrangement,[15] which showed identical spectroscopic properties with naturally occurring alcyonol-C,[26] a cembranoid from the red sea soft coral *Alcyomum utinomii*. The synthesis of naturally occurring **1** confirmed the stereochemical conclusions concerning the epoxy function of **1** made by Bowden in 1983.

Synthesis of (natural) (−)-7,8-epoxy-7,8-dihydrocembrene-C

Outlined in Scheme 5 is the enantioselective synthesis of **2**, which is analogous to the synthesis of **1** described above. Phosphono ester **21** was prepared from the corresponding homogeranyl iodide[19] in 78% yield and was subjected to regioselective epoxide formation *via* the bromohydrin intermediate (NBS, K_2CO_3, MeOH)[27] to give epoxide **22** in 72% yield, which was coupled with aldehyde **23**[28] by using LDA as base to give ester **24** as a 1 : 1 mixture of *E* and *Z* isomers in 61% yield. Treatment of **24** with $LiClO_4$ in benzene to give ketone **25** was followed by acidic hydrolysis and MnO_2 oxidation to yield keto aldehyde **6** (71%, 2 steps from **25**), which was cyclized following the procedure described above to afford the desired *Z*-form ester **26a** along with its *E* isomer in the ratio 1 : 1 in 42% yield after column chromatography on silica gel. Hydrolysis of ester **26a** produced the corresponding acid **26b**, which is identical spectroscopically with naturally occurring echinoic acid,[29] a newly identified cembranoid from the southern American folk medicinal plant *Echinodorus grandiflorus*. $LiAlH_4$ reduction of ester **26a** was followed by Sharpless asymmetric epoxidation with L-(+)-DET to give the epoxide **27** (82%, 2 steps). The title compound **2** was obtained after the usual iodination of **27** and subsequent $NaBH_3CN$ reductive dehalogention in an overall yield of 80% and 95% ee as determined by high-field (400 MHz) ^{1}H NMR analysis of the corresponding Mosher's ester. The synthetic **2** showed identical spectral data with those of natural product **2** as reported.[9] The specific optical rotation of synthetic **2** {$[\alpha]_D^{18}$ −25.2 (*c* 0.21 in $CHCl_3$)} is comparable to that of the natural product {$[\alpha]_D$ −22.5 (*c* 0.19 in $CHCl_3$)}. The configuration of the 7,8-epoxide function of natural product **2** is assigned as (7*R*,8*R*).

In summary, the first enantioselective total syntheses of (+)-11,12-epoxy-11,12-dihydrocembrene-C **1** and (−)-7,8-epoxy-7,8-dihydrocembrene-C **2** have been accomplished *via* a macro-olefination strategy by using titanium-mediated McMurry coupling as the key step and Sharpless asymmetric epoxidation for the introduction of chiral epoxide functions, through which we are able to confirm the absolute stereochemistry of **1** as (11*S*,12*S*) assigned two decades ago by Bowden, and to postulate the configuration of **2** as (7*R*,8*R*).

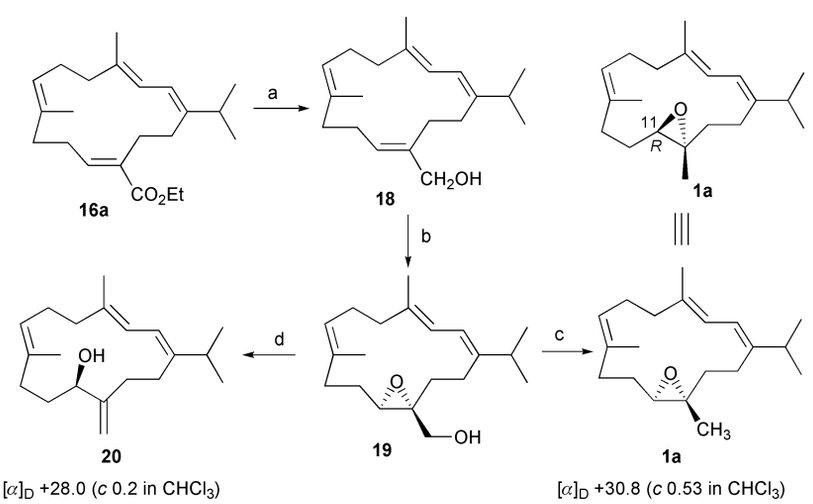


Scheme 3 *Reagents*, *conditions* (*and yields*): a) $LiAlH_4$, Et_2O, rt (92%); b) $Ti(O^iPr)_4$, D-(−)-DET, *t*-BuOOH, −20 °C (85%); c) (1) Ph_3P, I_2, imidazole, Py, Et_2O–CH_3CN (5 : 3), 0 °C (90%); (2) $NaBH_3CN$, HMPA, THF, 60 °C (90%).

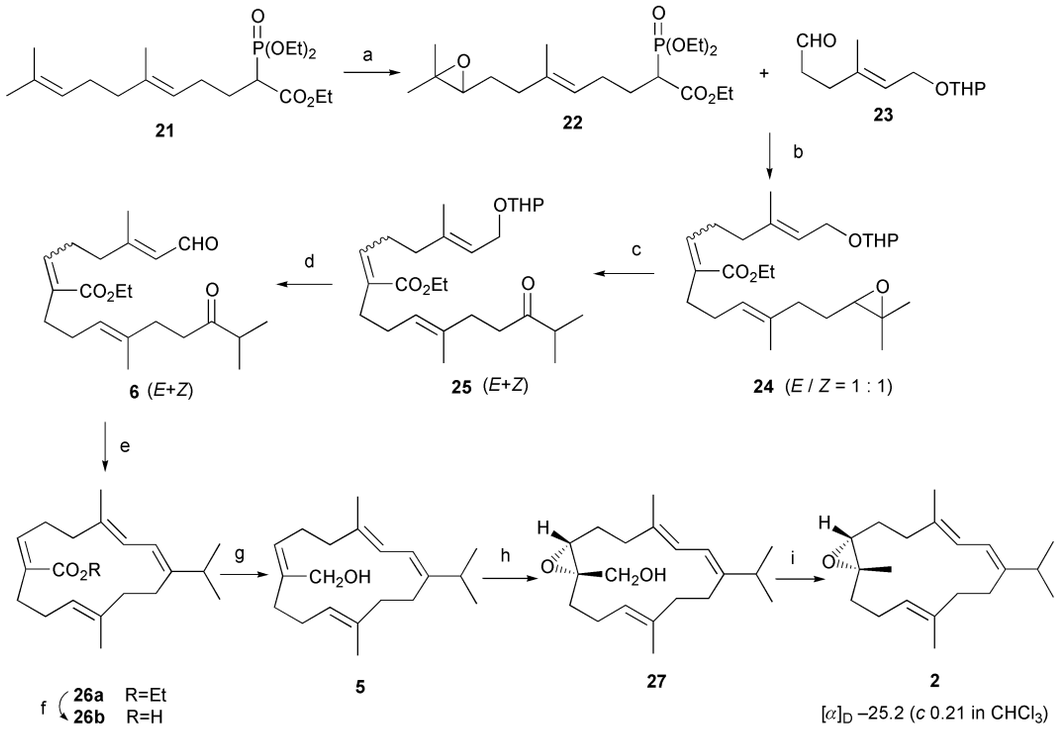
Experimental

General procedure

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-80 or AM-400 spectrometer for samples in $CDCl_3$ solution using $SiMe_4$ as internal reference. IR spectra were obtained using an FT-170SX spectrophotometer. Low-resolution mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV, and signals are given in *m*/*z* with relative intensity (%) in brackets. High-resolution mass specra (HRMS) were determined on a Bruker Daltonics APEXII 47e Fourier Transfer spectrometer with any of EI, CI, FAB, SIMS or MALDI ionization methods. Optical rotation measurements were carried out on a JASCO 20C polarimeter. All solvents were freshly purified and dried by standard techniques prior to use. Organic extractive phases were dried over anhydrous $MgSO_4$. Purification of products was performed by flash column chromatography (FCC) on silica gel (200–300 mesh) purchased from Qing Dao Marine Chemical Co. (Qingdao, China), and eluting with a solvent mixture (v/v) of petroleum spirit (60–90 °C) (PS) and ethyl acetate (EA).



Scheme 4 *Reagents*, *conditions* (*and yields*): a) $LiAlH_4$, Et_2O, rt (92%); b) $Ti(O^iPr)_4$, D-(−)-DET, *t*-BuOOH, −20 °C (85%); c) (1) Ph_3P, I_2, imidazole, Py, Et_2O–CH_3CN (5 : 3), 0 °C (90%); (2) $NaBH_3CN$, HMPA, THF, 60 °C (92%); d) Ph_3P, I_2, Py, Et_2O–CH_3CN (5 : 4), 0 °C; then water, 38 °C (91%).



Scheme 5 *Reagents*, *conditions* (*and yields*): a) (1) NBS, THF–water, 0 °C; (2) K_2CO_3, MeOH, 23 °C (72%); b) LDA, −78 °C, 30 min; then aldehyde **23**, −78 to 23 °C (61%); c) $LiClO_4$, C_6H_6, reflux (75%); d) (1) *p*-TsOH, MeOH, 23 °C; (2) MnO_2, *n*-hexane, 23 °C (71%); e) $TiCl_4$, Zn, THF, reflux (42%); f) KOH, EtOH–water, reflux (90%); g) $LiAlH_4$, Et_2O, 23 °C (90%); h) $Ti(O^iPr)_4$, L-(+)-DET, *t*-BuOOH, −20 °C (92%); i) (1) Ph_3P, I_2, imidazole, Py, Et_2O–CH_3CN (5 : 3), 0 °C; (2) $NaBH_3CN$, HMPA, THF, 60 °C (80%).

(4*E*,8*E*)-10-Acetoxy-4,8-dimethyldeca-4,8-dienal 9

To a solution of alcohol **8**[15] (4.93 g, 23.25 mmol) in ethyl vinyl ether (27 mL) was added $Hg(OAc)_2$ (3.0 g, 9.43 mmol, freshly recrystallized from anhydrous EtOH). The reaction mixture was refluxed for 24 h, cooled to room temperature and extracted with Et_2O (3 × 50 mL). The organic phases were washed successively with water and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 15 : 1) to afford the vinyl ether intermediate (4.6 g, 83%) as a colorless oil.

The vinyl ether (3.28 g, 13.78 mmol) was heated in a sealed tube under Ar atmosphere at 110 °C for 1 h. The crude product was purified by FCC (PS–EA 8 : 1) to afford the aldehyde **9** (2.95 g, 90%) as a colorless oil, ν_{max}(film)/cm^{-1} 2928, 2858, 2721, 1736, 1445, 1377, 1234, 1023 and 954; δ_H (80 MHz; $CDCl_3$) 9.77 (1H, t, *J* 1.6 Hz, CHO), 5.35 (1H, t, *J* 6.8 Hz, CH=), 5.14 (1H, t, *J* 6.4 Hz, CH=), 4.60 (2H, d, *J* 6.8 Hz, CH_2OAc), 2.25–2.54 (4H, m, 2 × CH_2), 2.07 (3H, s, CH_3CO), 1.95–2.14 (4H, m, 2 × CH_2), 1.71 (3H, s, CH_3), 1.63 (3H, s, CH_3); *m*/*z* (EI) 196 (M − 43, 0.2%), 178 (1), 163 (1.2), 134 (4), 119 (5), 93 (21), 67 (19), 55 (26) and 43 (100).

Ethyl 2-(diethoxyphosphoryl)-6-methylhept-5-enoate 11

To a stirred suspension of NaH (80%, 920 mg, 30 mmol) in anhydrous DMF (20 mL) was added dropwise a solution of ethyl (diethoxyphosphoryl)acetate[20] (4.45 mL, 22 mmol) in DMF (10 mL). The mixture was stirred at room temperature for 2 h and a solution of homoprenyl iodide **10**[19] (4.2 g, 20 mmol) was added. The resulting solution was stirred at 60 °C for 6 h and partitioned between Et_2O (20 mL) and water (10 mL). The reaction mixture was extracted with Et_2O (3 × 50 mL). The organic phases were washed successively with water and brine, and dried. Evaporation of the solvent was followed by FCC (PS–EA 3 : 1) to afford the phosphono ester **11** (5.44 g, 88%) as a colorless oil, ν_{max}(film)/cm^{-1} 2983, 2935, 1734, 1445, 1258, 1031 and 969; δ_H (80 MHz; $CDCl_3$) 5.01 (1H, t, *J* 7.2 Hz, CH=), 3.93–4.30 (6H, m, 3 × CH_2), 2.70–3.10 (1H, m, CH), 1.90–2.16 (4H, m, 2 × CH_2), 1.64 (3H, s, CH_3), 1.54 (3H, s, CH_3) and 1.16–1.38 (9H, m, 3 × CH_3); *m*/*z* (EI) 306 (M$^+$, 10%), 261 (12), 224 (100), 197 (82), 169 (31), 152 (84), 123 (44), 109 (32), 81 (51), 67 (29), 55 (52) and 41 (91).

Ethyl (5*E*)-2-(diethoxyphosphoryl)-6,10-dimethylundeca-5,9-dienoate 21

Phosphono ester **21** was similarly prepared from homogeranyl iodide[19] by alkylation with triethyl phosphonoacetate[20] in 78% yield, δ_H (80 MHz; $CDCl_3$) 4.90–5.05 (2H, m, 2 × CH=), 3.86–4.24 (6H, m, 3 × CH_2), 2.64–3.08 (1H, m, CH), 1.78–2.16 (8H, m, 4 × CH_2), 1.58 (3H, s, CH_3), 1.49 (6H, s, 2 × CH_3) and 1.10–1.31 (9H, m, 3 × CH_3).

Ethyl 2-(diethoxyphosphoryl)-5,6-epoxy-6-methylheptanoate 12

To a solution of phosphono ester **11** (3.06 g, 10 mmol) in 25 mL of CH_2Cl_2 was added MCPBA (70 wt%; 2.71 g, 11 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was extracted with Et_2O (3 × 50 mL), and the extract was washed 5% aq. NaOH (20 mL), saturated aq. $NaHCO_3$ (10 mL), water, and brine in turn, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 3 : 1) to give the epoxy phosphonate **12** (3.0 g, 93%) as a colorless oil, ν_{max}(film)/cm^{-1} 2982, 2933, 1733, 1450, 1374, 1254, 1050 and 1025; δ_H (80 MHz; $CDCl_3$) 4.14 (6H, m, 3 × CH_2), 2.80–3.10 (1H, m, CH), 2.68 (1H, t, *J* 6.4 Hz, epoxy H), 1.86–2.12 (2H, m, CH_2), 1.47–1.67 (2H, m, CH_2), 1.18–1.40 (9H, m, 3 × CH_3) and 1.95–2.14 (6H, s, 2 × CH_3); *m*/*z* (EI) 322 (M$^+$, 0.3%), 307 (M − 15, 44), 277 (14), 191 (62), 163 (60), 151 (25), 123 (57), 109 (59), 81 (100), 59 (75), 55 (60), 43 (98) and 41 (97).

Ethyl (5*E*)-2-(diethoxyphosphoryl)-9,10-epoxy-6,10-dimethylundec-5-enoate 22

Epoxy phosphonate **22** was prepared by regioselective epoxidation[27] of phosphono ester **21** in 72% yield, ν_{max}(film)/cm^{-1} 2980, 2932, 1734, 1447, 1375, 1255, 1024 and 966; δ_H (80 MHz; $CDCl_3$) 5.13 (1H, t, *J* 6.4 Hz, CH=), 3.96–4.35 (6H, m,

3 × CH_2), 2.84–3.10 (1H, m, CH), 2.70 (1H, t, *J* 6.3 Hz, epoxy H), 1.88–2.21 (6H, m, 3 × CH_2), 1.65–1.80 (2H, m, CH_2), 1.60 (3H, s, CH_3) and 1.20–1.42 (15H, m, 5 × CH_3); *m*/*z* (EI) 390 (M^+, 0.2%), 375 (0.1), 347 (0.5), 319 (2), 305 (12), 281 (1), 258 (4), 224 (33), 197 (39), 179 (11), 152 (38), 135 (11), 109 (40), 81 (56), 59 (76), 43 (68) and 41 (100).

(2*E*,6*E*)-1-Acetoxy-14,15-epoxy-11-ethoxycarbonyl-3,7,15-trimethylhexadeca-2,6,10-triene 13

To a stirred solution of lithium diisopropylamide (LDA) (2 M in THF; 5.12 mL, 10.24 mmol) in 10 mL of anhydrous THF was added a solution of phosphono ester **12** (3.0 g, 9.32 mmol) in THF (6 mL) over a period of 5 min under Ar atmosphere at −78 °C. After stirring of this mixture for 45 min at −78 °C, a solution of aldehyde **9** (2.22 g, 9.32 mmol) in THF (6 mL) was added over a period of 10 min. The resulting mixture was stirred at −78 °C for 30 min and then allowed to warm to room temperature gradually over a period of 6 h. Saturated aq. NH_4Cl (10 mL) was then added, the mixture was extracted with Et_2O (3 × 50 mL), and the combined extracts were washed successively with water and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 8:1) to give **13** as a mixture of *E* and *Z* isomers (*E* + *Z*, ≈ 1:1) (2.74 g, 72%) as a colorless oil, ν_{max}(film)/cm^{-1} 2966, 2930, 1739, 1710, 1641, 1447, 1378, 1234, 1187, 1025 and 956; δ_H (400 MHz; $CDCl_3$) 6.79 (0.5H, t, *J* 7.3 Hz, *E* CH=), 5.93 (0.5H, t, *J* 7.3 Hz, *Z* CH=), 5.34 (1H, t, *J* 7.1 Hz, CH=), 5.13 (1H, t, *J* 6.7 Hz, CH=), 4.58 (2H, d, *J* 7.1 Hz, C*H*$_2$OAc), 4.20 (2H, q, *J* 7.2 Hz, CH_2O), 2.72 (1H, t, *J* 6.3 Hz, epoxy H), 2.05–2.56 (10H, m, 5 × CH_2), 2.06 (3H, s, CH_3CO), 1.70 (3H, s, CH_3), 1.65–1.70 (2H, m, CH_2), 1.61 (3H, s, CH_3), 1.31 (3H, t, *J* 7.2 Hz, CH_3), 1.30 (3H, s, CH_3) and 1.25 (3H, s, CH_3); *m*/*z* (EI) 406 (M^+, 0.1%), 391 (0.1), 346 (M − AcOH, 0.1), 300 (0.9), 272 (0.6), 232 (3.4), 212 (4.7), 189 (2.4), 161 (4), 138 (5), 119 (10), 107 (10), 93 (20), 67 (19) and 43 (100) [Found (HRMS) (MALDI): M + Na^+, 429.2616. $C_{24}H_{38}NaO_5$ requires *M* + *Na*, 429.2611].

(2*E*,10*E*)-14,15-Epoxy-7-ethoxycarbonyl-3,11,15-trimethyl-1-(tetrahydropyran-2-yl)hexadeca-2,6,10-triene 24

Epoxide **24** was prepared by the Wadsworth–Horner–Emmons coupling of **22** with aldehyde **23**,[28] following the procedure described above as for **13**, an *E*/*Z* mixture (1:1) in 61% yield, ν_{max}(film)/cm^{-1} 2939, 2869, 1709, 1642, 1447, 1380, 1182, 1117, 1025, 905 and 870; δ_H (400 MHz; $CDCl_3$) 6.73 (0.5H, t, *J* 7.2 Hz, *E* CH=), 5.84 (0.5H, t, *J* 7.2 Hz, *Z* CH=), 5.40 (1H, t, *J* 6.9 Hz, CH=), 5.20 (1H, t, *J* 7.4 Hz, CH=), 4.62 (1H, s, OCHO), 4.25 (1H, dd, *J* 6.3 and 11.8 Hz, OC*H*$_2$CH=), 4.19 (2H, q, *J* 7.0 Hz, CH_2O), 4.03 (1H, dd, *J* 7.3 and 11.8 Hz, OC*H*$_2$CH=), 3.89 (1H, m, OCH_2), 3.52 (1H, m, OCH_2), 2.71 (1H, t, *J* 6.2 Hz, epoxy H), 2.34–2.40 (4H, m, 2 × CH_2), 2.09–2.17 (6H, m, 3 × CH_2), 1.54–1.72 (8H, m, 4 × CH_2), 1.70 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.30 (3H, t, *J* 7.0 Hz, CH_3), 1.31 (3H, s, CH_3) and 1.26 (3H, s, CH_3); *m*/*z* (EI) 363 (M − 85, 0.05%), 346 (0.08), 300 (0.54), 278 (0.2), 260 (0.3), 232 (0.7), 193 (2), 161 (1.6), 119 (4.3), 93 (8.6), 85 (100), 71 (18), 67 (24), 57 (18), 55 (17), 43 (42) and 41 (33).

(2*E*,6*E*)-1-Acetoxy-11-ethoxycarbonyl-3,7,15-trimethyl-14-oxohexadeca-2,6,10-triene 14

To a solution of epoxide **13** (*E* + *Z*, 1.22 g, 3.0 mmol) in 80 mL of dry benzene was added freshly dried $LiClO_4$ powder (330 mg) under Ar atmosphere at 80 °C for 1.5 h. The mixture was extracted with Et_2O (3 × 50 mL) and the combined extracts were washed successively with water and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 5:1) to give an inseparable mixture of geometric isomers of ketone **14** (*E* + *Z*, ≈ 1:1) (980 mg, 81%) as a colorless oil, ν_{max}(film)/cm^{-1} 2970, 2930, 1740, 1710, 1644, 1445, 1378, 1233, 1024 and 955; δ_H (400 MHz; $CDCl_3$) 6.76 (0.5H, t, *J* 7.4 Hz, *E* CH=), 5.93 (0.5H, t, *J* 7.3 Hz, *Z* CH=), 5.34 (1H, t, *J* 7.1 Hz, CH=), 5.10 (1H, t, *J* 7.6 Hz, CH=), 4.58 (2H, d, *J* 7.1 Hz, C*H*$_2$OAc), 4.18 (2H, q, *J* 7.2 Hz, CH_2O), 2.49–2.79 (6H, m, 3 × CH_2), 2.30 (1H, q, *J* 7.2 Hz, C*H*Me_2), 2.03–2.13 (6H, m, 3 × CH_2), 2.05 (3H, s, CH_3CO), 1.71 (3H, s, CH_3), 1.61 and 1.59 (3H, s, *Z* and *E* 7-CH_3), 1.30 (3H, t, *J* 7.2 Hz, CH_3) and 1.08 (6H, d, *J* 7.2 Hz, 2 × CH_3); *m*/*z* (EI) 360 (M − EtOH, 0.05%), 346 (M − AcOH, 0.2), 300 (1.5), 257 (0.2), 232 (5), 189 (3), 161 (3), 147 (4), 119 (8), 93 (16), 71 (21), 67 (13), 55 (12) and 43 (100) [Found (HRMS) (MALDI): M + Na^+, 429.2616. $C_{24}H_{38}NaO_5$ requires *M* + *Na*, 429.2611].

(2*E*,10*E*)-7-Ethoxycarbonyl-3,11,15-trimethyl-14-oxo-1-(tetrahydropyran-2-yloxy)hexadeca-2,6,10-triene 25

Ketone **25** was prepared by $LiClO_4$-mediated rearrangement, in an analogous procedure to that described above for **14**, as a geometric mixture (*E*/*Z*, 1:1) in 75% yield, ν_{max}(film)/cm^{-1} 2932, 2872, 1710, 1639, 1444, 1378, 1115 and 1024; δ_H (400 MHz; $CDCl_3$) 6.72 (0.5H, t, *J* 7.2 Hz, *E* CH=), 5.83 (0.5H, t, *J* 7.2 Hz, *Z* CH=), 5.39 (1H, t, *J* 6.4 Hz, CH=), 5.15 (1H, t, *J* 6.4 Hz, CH=), 4.62 (1H, s, OCHO), 4.15–4.30 (2H, m, CH_2O), 4.20 (1H, dd, *J* 6.8 and 12.0 Hz, OC*H*$_2$CH=), 4.02 (1H, dd, *J* 7.4 and 12.0 Hz, OC*H*$_2$CH=), 3.89 (1H, m, OCH_2), 3.53 (1H, m, OCH_2), 2.46–2.63 (3H, m, CH_2, CH), 2.08–2.32 (10H, m, 5 × CH_2), 1.54–1.83 (6H, m, 3 × CH_2), 1.68 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.25–1.31 (3H, m, CH_3) and 1.09 (6H, d, *J* 6.8 Hz, 2 × CH_3); *m*/*z* (EI) 363 (M − 85, 0.7%), 346 (1.1), 300 (5.4), 273 (1.2), 260 (3), 228 (2.8), 214 (4), 193 (6.7), 153 (6), 119 (9), 93 (11), 85 (100), 71 (47), 67 (32), 55 (25), 43 (70) and 41 (45) [Found (HRMS) (P-SIMS-Gly): M + 1^+, 449.3246. $C_{27}H_{45}O_5$ requires *M* + 1, 449.3261].

(2*E*,6*E*)-11-Ethoxycarbonyl-3,7,15-trimethyl-14-oxohexadeca-2,6,10-trienal 4

A mixture of acetate **14** (725 mg, 1.786 mmol) and powdered K_2CO_3 (254 mg, 1.84 mmol) in methanol (5 mL) was stirred vigorously at room temperature for 2 h. The reaction mixture was added to water (4 mL) and extracted with Et_2O (3 × 50 mL), then the combined organic phases were washed successively with water and brine, then dried. Evaporation of the solvent in vacuum gave the crude product, which without further purification was taken up in *n*-hexane (20 mL) and treated with active manganese dioxide [1.165 g, MnO_2 on silica gel (67 wt %), 8.93 mmol]. The resulting suspension was stirred for 24 h at room temperature, diluted with Et_2O (50 mL), filtered through a short pad of silica gel, and the resulting filtrate was concentrated in vacuum and purified by FCC to afford the keto aldehyde **4** (*E* + *Z*, ≈ 1:1) (466 mg, 72%) as a colorless oil. The *E* and *Z* isomers (1:1) were separated carefully by silica gel (300–400 mesh) column chromatography (PS–Et_2O 8:1). **4*Z***: ν_{max}(film)/cm^{-1} 2972, 2933, 1709, 1674, 1443, 1381, 1267, 1118 and 112; δ_H (400 MHz; $CDCl_3$) 9.99 (1H, d, *J* 8.1 Hz, CHO), 5.92 (1H, t, *J* 7.3 Hz, CH=), 5.88 (1H, d, *J* 8.1 Hz, CH=), 5.10 (1H, t, *J* 6.7 Hz, CH=), 4.21 (2H, q, *J* 7.1 Hz, CH_2O), 2.47–2.61 (6H m, 3 × CH_2), 2.25–2.35 (1H, m, CH), 2.17 (3H, s, CH_3), 2.15–2.25 (4H, m, 2 × CH_2), 2.04–2.15 (2H, m, CH_2), 1.60 (3H, s, CH_3), 1.30 (3H, t, *J* 7.1 Hz, CH_3) and 1.08 (6H, d, *J* 7.1 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 213.7, 191.2, 167.6, 163.6, 142.9, 135.7, 130.8, 127.4, 123.1, 60.1, 40.9, 40.5, 39.9, 39.0, 29.0, 28.0, 27.0, 25.6, 18.1, 17.6, 15.9 and 14.3; *m*/*z* (EI) 316 (M − EtOH, 0.2%), 298 (0.8), 279 (2.3), 233 (15), 166 (12), 138 (20), 119 (18), 93 (20), 71 (66), 55 (45) and 43 (100) [Found (HRMS) (MALDI): M + Na^+, 385.2359. $C_{22}H_{34}NaO_4$ requires *M* + *Na*, 385.2349]. **4*E***: δ_H (400 MHz; $CDCl_3$) 9.99 (1H, d, *J* 8.0 Hz, CH=), 6.74 (1H, t, *J* 7.4 Hz, CH=), 5.88 (1H, d, *J* 8.0 Hz, CH=), 5.11 (1H, t, *J* 6.7 Hz, CH=), 4.20 (2H, q, *J* 7.3 Hz, CH_2O), 2.49–2.61 (6H, m, 3 × CH_2), 2.15–2.31 (5H, m, 2 × CH_2, CH), 2.18 (3H, s, CH_3), 2.06–2.15 (2H, m, CH_2), 1.62

(3H, s, CH_3), 1.30 (3H, t, *J* 7.3 Hz, CH_3) and 1.08 (6H, d, *J* 6.8 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 213.9, 191.2, 167.5, 163.5, 142.9, 135.3, 131.2, 127.4, 123.1, 60.4, 40.7, 40.4, 39.4, 38.4, 29.0, 28.0, 27.0, 25.6, 18.1, 17.6, 16.0 and 14.3.

(2*E*,10*E*)-7-Ethoxycarbonyl-3,11,15-trimethyl-14-oxohexadeca-2,6,10-trienal 6

Keto aldehyde **6** was prepared by standard deprotection of the THP ether, followed by MnO_2 oxidation of the resulting allylic alcohol, in 71% yield. The *E* and *Z* isomers (1 : 1) were separated carefully by silica gel (300–400 mesh) column chromatography (PS–Et_2O 8 : 1). **6*Z***: ν_{max}(film)/cm^{-1} 2938, 2875, 1708, 1674, 1637, 1443, 1373, 1267, 1098 and 1025; δ_H (400 MHz; $CDCl_3$) 9.99 (1H, d, *J* 8.2 Hz, CHO), 5.89 (1H, d, *J* 8.2 Hz, CH=), 5.80 (1H, t, *J* 7.4 Hz, CH=), 5.10 (1H, t, *J* 6.4 Hz, CH=), 4.21 (2H, q, *J* 7.2 Hz, CH_2O), 2.58–2.70 (3H, m, CH_2 + CH), 2.47–2.53 (2H, m, CH_2), 2.31–2.42 (4H, m, 2 × CH_2), 2.19–2.24 (2H, m, CH_2), 2.19 (3H, s, CH_3), 2.05–2.14 (2H, m, CH_2), 1.66 (3H, s, CH_3), 1.31 (3H, t, *J* 7.2 Hz, CH_3) and 1.09 (6H, d, *J* 6.7 Hz, 2 × CH_3); *m*/*z* (EI) 362 (M^+, 2.3%), 333 (0.3), 316 (M − EtOH, 2.4), 299 (1.5), 277 (0.7), 231 (2), 209 (3.5), 193 (6), 163 (10), 153 (8), 135 (12), 107 (11), 91 (24), 71 (32), 67 (30), 55 (35), 43 (100) and 41 (53). **6*E***: δ_H (400 MHz; $CDCl_3$) 10.01 (1H, d, *J* 8.2 Hz, CHO), 6.68 (1H, t, *J* 7.4 Hz, CH=), 5.89 (1H, d, *J* 8.2 Hz, CH=), 5.15 (1H, t, *J* 6.4 Hz, CH=), 4.20 (2H, q, *J* 7.1 Hz, CH_2O), 2.58–2.76 (1H, m, CH), 2.51–2.55 (2H, m, CH_2), 2.31–2.40 (6H, m, 3 × CH_2), 2.18–2.29 (2H, m, CH_2), 2.20 (3H, s, CH_3), 2.06–2.11 (2H, m, CH_2), 1.60 (3H, s, CH_3), 1.30 (3H, t, *J* 7.1 Hz, CH_3) and 1.09 (6H, d, *J* 6.9 Hz, 2 × CH_3).

Ethyl (1*Z*,5*E*,9*E*,11*E*)-12-isopropyl-5,9-dimethylcyclotetradeca-1,5,9,11-tetraenecarboxylate 15a and its 1*E*-isomer 16a

To anhydrous THF (30 mL) was added dropwise $TiCl_4$ (1.94 mL, 18.2 mmol) at −78 °C with vigorous stirring under Ar atmosphere over a period of 5 min. After removal of the cooling bath, the resulting suspension was treated with zinc powder (2.89 g, 44.5 mmol) and heated to reflux for 2 h. A dilute solution of keto aldehyde **4** (215 mg, 0.594 mmol) in anhydrous THF (24 mL) was syringed in slowly over a period of 6 h. After the reaction mixture had been refluxed for an additional 2 h, then cooled to room temperature, 20% aq. K_2CO_3 (5 mL) was added. The resulting suspension was extracted with Et_2O (4 × 50 mL) and the combined organic phases were washed successively with saturated aq. $NaHCO_3$, water, and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC to give the cyclized esters **15a** and **16a** (94 mg, 48%) as a colorless oil. The *E* and *Z* isomers (1 : 1) were separated carefully by silica gel (300–400 mesh) column chromatography (PS–Et_2O 100 : 1). *Z*-Isomer **15a**: ν_{max}(film)/cm^{-1} 2956, 2869, 1709, 1640, 1453, 1375, 1264, 1182, 1100 and 1033; δ_H (400 MHz; $CDCl_3$) 6.01 (1H, d, *J* 11.2 Hz, CH=), 5.90 (1H, d, *J* 11.2 Hz, CH=), 5.82 (1H, t, *J* 6.7 Hz, CH=), 5.11 (1H, t, *J* 6.4 Hz, CH=), 4.18 (2H, q, *J* 6.9 Hz, CH_2O), 2.61 (2H, m, CH_2), 2.15–2.38 (11H, m, 5 × CH_2, CH), 1.74 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.30 (3H, t, *J* 6.9 Hz, CH_3) and 1.03 (6H, d, *J* 6.8 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 168.4, 146.3, 142.6, 134.9, 134.0, 131.8, 125.4, 121.8, 118.7, 59.9, 39.2, 38.6, 33.8, 30.5, 28.6, 26.1, 25.1, 22.1, 22.0, 16.9, 15.8 and 14.3; *m*/*z* (EI) 330 (M^+, 4.5%), 315 (1.2), 287 (5), 257 (7.4), 241 (5), 227 (4), 213 (1), 189 (10), 161 (20), 147 (26), 121 (67), 105 (64), 93 (85), 91 (86), 81 (69), 67 (62), 55 (89), 43 (60) and 41 (100) [Found (HRMS) (EI): M^+, 330.2559. $C_{22}H_{34}O_2$ requires *M*, 330.2553]. *E*-Isomer **16a**: δ_H (400 MHz; $CDCl_3$) 6.75 (1H, t, *J* 7.9 Hz, CH=), 6.01 (1H, d, *J* 10.7 Hz, CH=), 5.93 (1H, d, *J* 10.7 Hz, CH=), 5.16 (1H, t, *J* 6.6 Hz, CH=), 4.18 (2H, q, *J* 7.2 Hz, CH_2O), 2.12–2.43 (13H, m, 6 × CH_2, CH), 1.73 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.30 (3H, t, *J* 7.2 Hz, CH_3) and 1.07 (6H, d, *J* 7.0 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 168.4, 146.6, 142.7, 135.4, 135.1, 132.8, 127.5, 120.2, 118.6, 60.2, 38.9, 37.8, 34.9, 30.7, 29.0, 27.3, 24.9, 22.1, 22.0, 18.0, 17.4 and 14.3.

Ethyl (1*Z*,5*E*,7*E*,11*E*)-8-isopropyl-5,11-dimethylcyclotetradeca-1,5,7,11-tetraenecarboxylate 26a

Cyclized ester **26a** was synthesized in an analogous way, as described above for **15a/16a**, in 42% yield, ν_{max}(film)/cm^{-1} 2960, 2927, 1709, 1642, 1445, 1379, 1261, 1103 and 1027; δ_H (400 MHz; $CDCl_3$) 5.96 (1H, d, *J* 10.8 Hz, CH=), 5.86 (1H, d, *J* 10.8 Hz, CH=), 5.65 (1H, t, *J* 6.8 Hz, CH=), 4.93 (1H, t, *J* 6.4 Hz, CH=), 4.13 (2H, q, *J* 7.4 Hz, CH_2O), 2.36–2.45 (1H, m, CH), 2.01–2.32 (12H, m, 6 × CH_2), 1.68 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.24 (3H, t, *J* 7.4 Hz, CH_3) and 0.98 (6H, d, *J* 6.7 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 168.1, 147.9, 144.7, 143.2, 136.2, 134.4, 124.5, 121.5, 118.4, 59.9, 39.6, 38.7, 34.5, 34.0, 28.0, 26.6, 25.3, 22.3, 22.0, 17.3, 16.6 and 14.4; *m*/*z* (EI) 330 (M^+, 8%), 315 (1), 287 (5), 257 (4), 241 (4), 219 (3), 194 (9), 161 (19), 121 (100), 105 (48), 93 (83), 91 (74), 67 (52), 55 (52), 43 (52) and 41 (89) [Found (HRMS) (EI): M^+. 330.2553. Calc. for $C_{22}H_{34}O_2$: *M*, 330.2553].

Crotocembraneic acid 15b

A mixture of ester **15a** (15 mg, 0.045 mmol) and KOH (20 mg, 0.36 mmol) in 3 mL of EtOH–water (1 : 1) was refluxed for 2 h. The solution was cooled to room temperature, diluted with Et_2O (5 mL), acidified with 5% aq. HCl, and stirred for 10 min at room temperature. The mixture was extracted with Et_2O (50 mL). The combined organic phases were washed successively with water and brine and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 3 : 1) to give the desired crotocembraneic acid (12 mg, 88%) as a colorless oil, ν_{max}(film)/cm^{-1} 2955, 2927, 1683, 1635, 1445, 1279, 1116, 1027 and 912; δ_H (400 MHz; $CDCl_3$) 6.02 (1H, d, *J* 10.9 Hz, CH=), 5.99 (1H, t, *J* 6.5 Hz, CH=), 5.90 (1H, d, *J* 10.9 Hz, CH=), 5.10 (1H, t, *J* 6.4 Hz, CH=), 2.68 (2H, m, CH_2), 2.16–2.46 (11H, m, 5 × CH_2, CH), 1.74 (3H, s, CH_3), 1.55 (3H, s, CH_3) and 1.03 (6H, d, *J* 6.7 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 172.4, 146.1, 145.7, 135.2, 134.0, 131.0, 125.8, 121.7, 118.8, 39.2, 38.5, 33.7, 33.6, 28.7, 26.5, 25.1, 22.1 (2C), 16.9 and 15.8; *m*/*z* (EI) 302 (M^+, 19%), 287 (2), 271 (1), 259 (5), 241 (2), 213 (3), 191 (10), 152 (23), 136 (80), 121 (100), 107 (32), 93 (80), 67 (34) and 41 (34).

Neocrotocembraneic acid 16b

Prepared in identical manner to its isomer **15b** in 90% yield, δ_H (400 MHz; $CDCl_3$) 6.90 (1H, t, *J* 8.0 Hz, CH=), 6.03 (1H, d, *J* 11.0 Hz, CH=), 5.93 (1H, d, *J* 11.0 Hz, CH=), 5.16 (1H, t, *J* 6.7 Hz, CH=), 2.16–2.40 (13H, m, 6 × CH_2, CH), 1.73 (3H, s, CH_3), 1.70 (3H, s, CH_3) and 1.07 (6H, d, *J* 6.7 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 172.6, 146.2, 145.7, 135.6, 134.8, 132.0, 127.8, 120.0, 118.6, 38.5, 37.7, 34.5, 30.5, 29.2, 26.5, 24.7, 22.1 (2C), 18.0 and 17.4.

Echinoic acid 26b

Echinoic acid **26b** was synthesized in an analogous way to that described above for **15b**, in 90% yield, ν_{max}(film)/cm^{-1} 2920, 2857, 1702, 1420, 1285, 1153, 1097 and 974; δ_H (400 MHz; $CDCl_3$) 6.08 (1H, d, *J* 11.6 Hz, CH=), 5.95 (1H, d, *J* 11.6 Hz, CH=), 5.70 (1H, t, *J* 8.4 Hz, CH=), 5.32 (1H, t, *J* 6.4 Hz, CH=), 2.75–2.88 (2H, m, CH_2), 2.00–2.42 (11H, m, 5 × CH_2, CH), 1.70 (3H, s, CH_3), 1.59 (3H, s, CH_3) and 1.09 (6H, d, *J* 7.0 Hz, 2 × CH_3); *m*/*z* (EI) 302 (M^+, 25%), 287 (2), 271 (1), 259 (6), 241 (2), 213 (5), 161 (11), 147 (20), 121 (70), 107 (74), 105 (65), 93 (100), 91 (75), 79 (60), 55 (59), 43 (62) and 41 (72).

(1*Z*,5*E*,9*E*,11*E*)-12-Isopropyl-5,9-dimethylcyclotetradeca-1,5,9,11-tetraenylmethanol 3

To a well stirred suspension of $LiAlH_4$ (16 mg, 0.42 mmol) in Et_2O (6 mL) was added dropwise a solution of ester **15a** (70 mg,

0.21 mmol) in Et_2O (6 mL) at 0 °C and the mixture was stirred at room temperature for 24 h. Methanol (0.1 mL) was added to decompose the excess of reagent and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed successively with 5% aq. HCl (2 × 10 mL), saturated aq. $NaHCO_3$ (10 mL), water, and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 4:1) to give the allylic alcohol **3** (56 mg, 92%) as a colorless oil, ν_{max}(film)/cm^{-1} 3357, 2956, 2928, 1668, 1456, 1377 and 1006; δ_H (400 MHz; $CDCl_3$) 6.06 (1H, d, *J* 10.8 Hz, CH=), 5.93 (1H, d, *J* 10.8 Hz, CH=), 5.26 (1H, t, *J* 6.8 Hz, CH=), 5.00 (1H, t, *J* 6.5 Hz, CH=), 4.05 (2H, s, CH_2O), 2.02–2.42 (13H, m, 6 × CH_2, CH), 1.74 (3H, s, CH_3), 1.52 (3H, s, CH_3) and 1.06 (6H, d, *J* 7.0 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 146.5, 138.4, 135.0, 133.8, 129.6, 125.1, 122.0, 118.6, 61.7, 39.3, 38.8, 33.6, 33.0, 28.7, 25.4, 24.3, 22.2, 21.2, 16.8 and 15.8; *m*/*z* (EI) 288 (M^+, 2.8%), 273 (0.9), 270 (0.7), 257 (4.2), 245 (5), 227 (4), 201 (3), 189 (5), 173 (5), 161 (13), 145 (16), 121 (41), 105 (53), 93 (68), 91 (67), 79 (56), 67 (43), 55 (65), 43 (57) and 41 (100) [Found (HRMS) (EI): M^+, 288.2446. $C_{20}H_{32}O$ requires *M*, 288.2448].

(1*E*,5*E*,9*E*,11*E*)-12-Isopropyl-5,9-dimethylcyclotetradeca-1,5,9,11-tetraenylmethanol 18

Prepared in identical manner to its isomer **3** in 92% yield, δ_H (400 MHz; $CDCl_3$) 6.07 (1H, d, *J* 11.1 Hz, CH=), 5.99 (1H, d, *J* 11.1 Hz, CH=), 5.44 (1H, t, *J* 7.6 Hz, CH=), 5.09 (1H, t, *J* 6.8 Hz, CH=), 4.00 (2H, s, CH_2O), 2.34 (1H, sept, *J* 6.8 Hz, C*H*Me_2), 2.09–2.24 (12H, m, 6 × CH_2), 1.74 (3H, s, CH_3), 1.70 (3H, s, CH_3) and 1.07 (6H, d, *J* 6.8 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 146.7, 139.3, 136.0, 135.1, 128.2, 127.2, 119.7, 118.7, 67.3, 39.2, 37.5, 34.8, 28.9, 28.7, 28.3, 24.8, 22.2 (2C), 18.2 and 17.8.

(1*Z*,5*E*,7*E*,11*E*)-8-Isopropyl-5,11-dimethylcyclotetradeca-1,5,7,11-tetraenylmethanol 5

Allylic alcohol **5** was synthesized in an analogous way to that described above for **3**, in 90% yield from **26a**, ν_{max}(film)/cm^{-1} 3358, 2956, 2928, 1668, 1456, 1377 and 1006; δ_H (400 MHz; $CDCl_3$) 6.00 (1H, d, *J* 11.3 Hz, CH=), 5.87 (1H, d, *J* 11.3 Hz, CH=), 5.20 (1H, t, *J* 7.4 Hz, CH=), 5.03 (1H, t, *J* 6.4 Hz, CH=), 3.95 (2H, s, CH_2O), 2.10–2.39 (13H, m, 6 × CH_2, CH), 1.75 (3H, s, CH_3), 1.60 (3H, s, CH_3) and 1.03 (6H, d, *J* 7.0 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 147.6, 138.3, 134.6, 133.6, 128.7, 124.8, 123.4, 118.0, 60.4, 39.6, 37.6, 34.9, 33.4, 29.7, 27.7, 25.3, 22.4, 21.2, 17.6 and 16.5; *m*/*z* (EI) 288 (M^+, 8%), 273 (1.3), 270 (0.6), 257 (1.6), 245 (3.2), 227 (4), 203 (6), 187 (4), 136 (31), 121 (64), 93 (74), 91 (60), 67 (47), 55 (71), 43 (55) and 41 (100) [Found (HRMS) (EI): M^+, 288.2456. $C_{20}H_{32}O$ requires *M*, 288.2448].

(1*S*,4*E*,6*E*,10*E*,14*S*)-1,14-Epoxy-4-isopropyl-7,11-dimethylcyclotetradeca-4,6,10-trienylmethanol 17

To a mixture of $Ti(O^iPr)_4$ (0.056 mL, 0.191 mmol), CaH_2 (2 mg), 4 Å molecular sieves (6 mg) and silica gel (2 mg) in 2 mL of dry CH_2Cl_2 was added D-(−)-DET (0.039 mL, 0.229 mmol) under Ar atmosphere at −20 °C. After stirring of this mixture for 10 min, a solution of the allylic alcohol **3** (55 mg, 0.191 mmol) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred for an additional 10 min and *t*-BuOOH (3.16 M in toluene; 0.121 mL, 0.382 mL) was added at −40 °C. After 8 h at −20 °C the mixture was treated with 1 mL of 10% aq. tartaric acid. After stirring for 1 h, the mixture was diluted by Et_2O (150 mL), washed successively with 5% aq. NaOH (2 × 10 mL), saturated aq. $NaHCO_3$ (15 mL), water, and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 3:1) to give the epoxy alcohol **17** (49 mg, 85%) as a colorless oil, $[\alpha]_D^{20}$ +68.7 (*c* 0.75 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3385, 2958, 2926, 1661, 1609, 1452, 1157, 1040 and 898; δ_H (400 MHz; $CDCl_3$) 5.95 (1H, d, *J* 10.6 Hz, CH=), 5.84 (1H, d, *J* 10.6 Hz, CH=), 5.22 (1H, t, *J* 6.7 Hz, CH=), 3.76 (1H, dd, *J* 6.6 and 11.8 Hz, C*H*OH), 3.64 (1H, dd, *J* 4.4 and 11.8 Hz, C*H*OH), 3.06 (1H, t, *J* 6.2 Hz, epoxy H), 2.02–2.34 (9H, m, 4 × CH_2, CH), 1.61–1.83 (4H, m, 2 × CH_2), 1.73 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.05 (3H, d, *J* 3.3 Hz, CH_3) and 1.03 (3H, d, *J* 3.3 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 146.7, 136.0, 133.2, 127.2, 120.9, 118.5, 63.4, 62.2, 60.5, 38.6, 36.8, 34.4, 33.7, 25.5, 23.9, 23.4, 22.4, 22.2, 17.2 and 15.0; *m*/*z* (EI) 304 (M^+, 9%), 286 (0.9), 273 (4.7), 255 (2.4), 243 (2.4), 215 (1.9), 193 (34), 175 (13), 133 (30), 121 (81), 107 (58), 93 (100), 67 (43), 55 (65) and 41 (67) [Found (HRMS) (EI): M^+, 304.2399. $C_{20}H_{32}O_2$ requires *M*, 304.2397].

Preparation and analysis of Mosher's ester

To a mixture of dicyclohexylcarbodiimide (DCC) (3.7 mg, 18 μmol) and epoxy alcohol **17** (5 mg, 16.4 μmol) in 0.5 mL of dry CH_2Cl_2 was added (*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (4.2 mg, 18 μmol) and a catalytic mount of 4-(dimethylamino)pyridine (DMAP). After stirring at room temperature for 24 h, the solution was evaporated in vacuum and the residue was directly chromatographed with PS–EA (15:1).

(1*S*,4*E*,6*E*,10*E*,14*R*)-1,14-Epoxy-4-isopropyl-7,11-dimethylcyclotetradeca-4,6,10-trienylmethanol 19

Prepared from allylic alcohol **18** in identical manner to **17**, in 85% yield, $[\alpha]_D^{23}$ +16.8 (*c* 1.4 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.99 (1H, d, *J* 10.7 Hz, CH=), 5.90 (1H, d, *J* 10.7 Hz, CH=), 5.18 (1H, t, *J* 6.6 Hz, CH=), 3.78 (1H, dd, *J* 4.3 and 12.2 Hz, C*H*OH), 3.60 (1H, dd, *J* 8.4 and 12.2 Hz, C*H*OH), 3.12 (1H, dd, *J* 4.0 and 8.4 Hz, epoxy H), 2.06–2.33 (9H, m, 4 × CH_2, CH), 1.80–1.88 (2H, m, CH_2), 1.73 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.47–1.59 (2H, m, CH_2) and 1.05 (6H, d, *J* 6.7 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 146.1, 135.7, 134.9, 126.3, 121.1, 118.7, 63.7, 61.0, 60.5, 38.6, 35.8, 35.0, 29.0, 28.4, 25.1, 24.7, 22.2, 22.0, 17.4 and 16.9.

(1*R*,4*E*,8*E*,10*E*,14*R*)-1,14-Epoxy-8-isopropyl-5,11-dimethylcyclotetradeca-4,8,10-trienylmethanol 27

Epoxy alcohol **27** was synthesized in an analogous way to that described above for **17**, in 92% yield from **5** with 95% ee, $[\alpha]_D^{20}$ −41.7 (*c* 0.35 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3400, 2960, 2926, 1660, 1610, 1452, 1160 and 1040; δ_H (400 MHz; $CDCl_3$) 6.04 (1H, d, *J* 10.8 Hz, CH=), 5.97 (1H, d, *J* 10.8 Hz, CH=), 5.08 (1H, t, *J* 6.4 Hz, CH=), 3.78 (1H, dd, *J* 6.5 and 11.8 Hz, C*H*OH), 3.63 (1H, dd, *J* 4.2 and 11.8 Hz, C*H*OH), 3.00 (1H, t, *J* 5.7 Hz, epoxy H), 2.04–2.34 (9H, m, 4 × CH_2, CH), 1.60–1.90 (4H, m, 2 × CH_2), 1.76 (3H, s, CH_3), 1.59 (3H, s, CH_3) and 1.06 (6H, d, *J* 6.5 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 148.2, 135.9, 133.7, 125.6, 121.8, 118.4, 63.1, 62.8, 61.8, 39.1, 35.8, 34.7, 32.3, 28.4, 25.0, 23.0, 22.3, 22.2, 22.1, 17.2 and 17.0; *m*/*z* (EI) 304 (M^+, 9%), 286 (1), 273 (5), 255 (3), 243 (2), 215 (2), 193 (34), 133 (30), 121 (82), 93 (100), 67 (43), 55 (65) and 41 (67).

(11*S*,12*S*)-11,12-Epoxy-11,12-dihydrocembrene-C 1

To a stirred solution of epoxy alcohol **17** (27 mg, 0.089 mmol) in dry Et_2O–CH_3CN (5:3; 2 mL) were added sequentially Ph_3P (35 mg, 0.133 mmol), imidazole (9 mg, 0.133 mmol), pyridine (0.021 mL, 0.266 mmol) and I_2 (33.8 mg, 0.133 mmol) at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C, diluted with Et_2O (50 mL), and washed successively with 20% aq. $Na_2S_2O_3$, water, and brine, and dried. Evaporation of the solvent in vacuum, followed by FCC (PS–EA 70:1) to give the epoxy iodide (33 mg, 90%) as a colorless oil. To a solution of this epoxy iodide (24 mg, 0.06 mmol) in THF (0.6 mL) were added HMPA (0.15 mL) and $NaBH_3CN$ (12 mg, 0.18 mg) at room temperature. The reaction mixture was stirred for 21 h at 60 °C under Ar atmosphere. The resulting mixture was diluted with

Et_2O (5 mL), washed successively with water and brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PS–EA 60:1) to give epoxide **1** (15 mg, 90%) as a colorless oil, $[\alpha]_D^{20}$ +109.1 (*c* 0.35 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2959, 2925, 1656, 1609, 1456, 1378, 1088 and 1024; δ_H (400 MHz; $CDCl_3$) 5.93 (1H, d, *J* 10.6 Hz, CH=), 5.84 (1H, d, *J* 10.6 Hz, CH=), 5.23 (1H, t, *J* 6.0 Hz, CH=), 2.88 (1H, t, *J* 6.2 Hz, epoxy H), 2.13–2.32 (9H, m, 4 × CH_2, CH), 1.99–2.05 (4H, m, 2 × CH_2), 1.72 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.04 (3H, d, *J* 2.8 Hz, CH_3) and 1.02 (3H, d, *J* 2.8 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 147.1, 135.9, 133.4, 127.1, 120.8, 118.4, 61.0, 60.4, 38.3, 36.9, 36.8, 34.1, 25.3, 24.5, 24.3, 22.3, 22.2, 18.0, 17.4 and 15.0; *m*/*z* (EI) 288 (M^+, 12%), 273 (3), 255 (2), 245 (5), 227 (3), 205 (3), 189 (5), 177 (41), 161 (12), 136 (32), 121 (95), 107 (60), 93 (100), 79 (54), 67 (43), 55 (48), 43 (67) and 41 (82) [Found (HRMS) (EI): M^+, 288.2440. Calc. for $C_{20}H_{32}O$: *M*, 288.2448].

(11*R*,12*S*)-11,12-Epoxy-11,12-dihydrocembrene-C 1a

Similarly prepared, from **19**, in 91% yield over the two steps, $[\alpha]_D^{23}$ +30.8 (*c* 0.53 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.99 (1H, d, *J* 11.4 Hz, CH=), 5.93 (1H, d, *J* 11.4 Hz, CH=), 5.16 (1H, t, *J* 6.6 Hz, CH=), 2.80 (1H, dd, *J* 4.3 and 8.0 Hz, epoxy H), 2.10–2.30 (12H, m, 6 × CH_2), 1.90–2.00 (1H, m, CH), 1.72 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.06 (3H, d, *J* 3.0 Hz, CH_3) and 1.04 (3H, d, *J* 3.0 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 146.7, 135.4, 135.0, 126.2, 121.0, 118.5, 65.8, 65.0, 38.4, 35.9, 35.0, 33.1, 29.7, 28.6, 25.7, 24.7, 22.4, 21.9, 17.4 and 17.3.

(7*R*,8*R*)-7,8-Epoxy-7,8-dihydrocembrene-C 2

7,8-Epoxy-7,8-dihydrocembrene-C **2** was synthesized in an analogous way to that described above for **1**, in 80% yield from **27**, $[\alpha]_D^{20}$ −25.2 (*c* 0.21 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2960, 2925, 1656, 1456, 1380, 1088 and 1024; δ_H (400 MHz; $CDCl_3$) 6.03 (1H, d, *J* 10.9 Hz, CH=), 5.97 (1H, d, *J* 10.9 Hz, CH=), 5.07 (1H, t, *J* 6.4 Hz, CH=), 2.85 (1H, t, *J* 5.6 Hz, epoxy H), 2.19–2.36 (8H, m, 4 × CH_2), 1.91–2.02 (5H, m, 2 × CH_2, CH), 1.77 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.27 (3H, s, CH_3) and 1.06 (6H, t, *J* 6.5 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 148.2, 135.6, 134.2, 125.5, 121.5, 118.4, 61.6, 60.1, 39.4, 37.5, 35.8, 34.9, 28.2, 25.8, 22.5, 22.3, 22.2, 17.8, 17.1 and 17.0; *m*/*z* (EI) 288 (M^+, 2.6%), 270 (0.9), 255 (0.8), 245 (3), 227 (3), 205 (4.5), 187 (3), 177 (3), 163 (10), 136 (46), 121 (93), 107 (60), 93 (100), 69 (61), 55 (54), 43 (83) and 41 (72) [Found (HRMS) (EI): M^+, 288.2443. Calc. for $C_{20}H_{32}O$: *M*, 288.2448].

Aclyonol-C 20

To a stirred solution of epoxy alcohol **19** (15 mg, 0.05 mmol) in dry Et_2O–CH_3CN (1.5:1.2 mL) were added sequentially Ph_3P (39.3 mg, 0.15 mmol), pyridine (0.016 mL, 0.2 mmol) and I_2 (19 mg, 0.075 mmol) at 0 °C. After the mixture had been stirred for 2 h at 0 °C, water (0.9 μL, 0.05 mmol) was added to the system. The reaction mixture was refluxed for 6 h at 38 °C, then 20% aq. $Na_2S_2O_3$ (0.5 mL) and saturated aq. $NaHCO_3$ (0.5 mL) were added to quench the reaction, and the organic layer was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed successively with 5% HCl (4 × 10 mL), saturated aq. $NaHCO_3$ (10 mL), water, and brine, and dried. Evaporation of the solvent gave a residue, which was flash chromatographed and eluted with PS–EA (6:1) to afford **20** (13 mg, 91%) as a colorless oil, $[\alpha]_D^{20}$ +28 (*c* 0.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3402, 3074, 2942, 2861, 1671, 1650, 1296, 1024 and 910; δ_H (400 MHz; $CDCl_3$) 5.96 (1H, d, *J* 11.0 Hz, CH=), 5.90 (1H, d, *J* 11.0 Hz, CH=), 5.17 (1H, t, *J* 6.8 Hz, CH=), 5.05 and 4.84 (2H, s, CH_2=), 4.18 (1H, t, *J* 4.4 Hz, C*H*OH), 2.44–2.48 (1H, m, C*H*Me_2), 2.30–2.36 (2H, m, CH_2), 2.19–2.25 (4H, m, 2 × CH_2), 2.02–2.10 (4H, m, 2 × CH_2), 1.92–1.96 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.59 (3H, s, CH_3) and 1.03 (6H, d, *J* 6.7 Hz, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 153.5, 146.4, 135.2, 134.1, 125.5, 121.8, 118.4, 108.4, 69.8, 39.4, 34.8, 34.6, 34.5, 33.6, 28.9, 25.4, 22.1, 21.8, 16.9 and 16.6; *m*/*z* (EI) 288 (M^+, 1.5%), 270 (1.9), 255 (2), 227 (4), 205 (3), 177 (41), 136 (32), 121 (30), 107 (41), 83 (100), 67 (43) and 43 (67).

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant No.: 20072012).

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